INVESTIGATING THE ROLE OF PARP INHIBITORS IN THE TREATMENT OF OVARIAN CANCER

Ph.D. Thesis booklet

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Budapest

2025

1. INTRODUCTION

Ovarian cancer (OC) is a major gynecologic malignancy, ranking third in frequency and second in mortality among gynecologic cancers, with poor prognosis in advanced stages. Epithelial ovarian cancer (EOC), particularly high-grade serous carcinoma (HGSC), accounts for 90% of OC cases and often originates in the fallopian tube fimbriae. Due to its asymptomatic nature and lack of effective screening, about 75% of HGSC cases are diagnosed at advanced stages. Standard treatment involves cytoreductive surgery followed by chemotherapy, but most patients eventually relapse or develop resistance. BRCA1/2 mutations and homologous recombination deficiency (HRD), present in approximately 50% of HGSC cases, have become key targets for therapy. PARP inhibitors (olaparib, rucaparib, niraparib) exploit HRD to induce synthetic lethality in tumor cells.

Angiogenesis is also critical in OC progression, and anti-angiogenic agents like bevacizumab target the VEGF pathway to disrupt tumor vascularization. Combining PARP inhibitors with anti-angiogenic agents has shown synergistic effects, including enhanced DNA damage and immune responses. This combination increases tumor sensitivity to PARP inhibition and improves progression-free and overall survival. However, current clinical guidelines still favor monotherapy with PARP inhibitors or chemotherapy over combination regimens.

2. OBJECTIVES

During my PhD. work I set up two goals, to make a comprehensive work:

2.1 Study I.

The object of my first study was to evaluate the survival benefits and potential adverse effects of PARP inhibitors by analyzing data from randomized controlled trials (RCTs), with a focus on outcomes across different patient subgroups.

2.2 Study II.

The object of my second study was to evaluate the efficacy and safety of combining PARP inhibitors with anti-angiogenic agents (AAAs) in the treatment of ovarian cancer, in comparison to PARP inhibitor monotherapy and standard chemotherapy.

3. METHODS

To ensure methodological rigor, both meta-analyses were planned using a PRISMA checklist and followed the MOOSE guidelines.

3.1. Study I.

A systematic literature search was performed from inception till April 13, 2022: during the process the electronic databases of MEDLINE (via PubMed), EMBASE, and Cochrane Library were used. The search terms included all types of PARPis and ovarian cancer-related terms. The reference lists of the eligible articles were manually reviewed to identify any additional potentially relevant trials.

All RCTs were marked as eligible which: (1) investigated patients who were diagnosed with advanced OC, peritoneum, or fallopian tube; (2) provided data on newly-diagnosed or recurrent cases in terms of OS, progression-free survival (PFS), or adverse events (AEs) (e.g. anaemia, thrombocytopenia, neutropenia, leukopenia, vomiting, fatigue, and nausea); (3) utilized PARP inhibitors as an intervention in monotherapy, maintenance therapy, or in combination with standard-of-care treatments. Studies got excluded that were: (1) phase I RCTs; (2) conference abstracts which did not show reliable data on study design; and (3) tested PARPis in a combination with other targeted therapeutic agents.

Two authors independently assessed the quality of all the included studies with the help of the Revised Cochrane risk-of-bias tool for RCTs (RoB 2).

3.2. Study II.

To find eligible articles, a systematic search was performed using 3 online databases: MEDLINE (via PubMed), EMBASE, and Cochrane Library. The databases got searched through from their inception until November 28, 2022. The search strategy used a combination of relevant keywords and Medical Subject Headings (MeSH) terms, including the

likes of "ovarian cancer," "PARP inhibitors," "anti-angiogenic agents," and "combination therapy”

In this part of the study as well, two authors independently assessed the quality of all the included studies with the help of the Revised Cochrane risk-of-bias tool for RCTs (RoB 2).

4. RESULTS

This section presents the results of two meta-analyses conducted during the PhD project, focusing on the efficacy and safety of PARP inhibitors (PARPis) alone and in combination with anti-angiogenic agents (AAAs) in ovarian cancer (OC).

4.1. Study I.

The first meta-analysis included data from 23 articles covering 16 trials with 5,815 patients, primarily assessing the impact of PARPis in recurrent and newly diagnosed OC cases. PARPis used as maintenance therapy significantly improved progression-free survival (PFS), particularly in patients with BRCA mutations, though improvements in overall survival (OS) were generally not statistically significant. Monotherapy with PARPis compared to chemotherapy showed no significant PFS benefit in the overall population but showed promise in BRCA-mutated patients. When PARPis were combined with chemotherapy and continued as maintenance, a significant PFS benefit was observed, especially in BRCA-mutated subgroups, though OS remained unaffected. Adverse events (AEs), particularly hematological toxicities and treatment-related discontinuations, were more common with PARPi use, especially in maintenance settings.

4.2. Study II.

The second meta-analysis included 7 RCTs and 2,157 patients, focusing on the efficacy and safety of combining PARPis with AAAs. In recurrent OC cases, the combination did not significantly improve PFS over PARPi monotherapy, and safety profiles were largely similar, except for a notable increase in the risk of hypertension. In newly diagnosed cases, however, the combination therapy showed a clear benefit in PFS across all BRCA subgroups. The overall quality of evidence for both analyses ranged from low to moderate, influenced by heterogeneity, open-label designs, and limited OS data.

5. CONCLUSION

The studies I carried out came to the following conclusions:

5.1 Study I.

PARPi's therapy showed superior PFS outcomes compared to control groups in the treatment of advanced OC cases across various settings. However, it is also associated with an increased risk of high-grade AEs. I would also like to emphasize that evaluating BRCA mutation and HRD status is crucial in guiding PARPi use. Patients with these genetic deficiencies tend to derive significant benefit from the maintenance PARPi usage.

5.2 Study II.

The combination therapy of PARPis and AAAs did not demonstrate a statistically significant benefit in the investigated populations when they were compared to PARPis or chemotherapy alone. The safety analysis indicated that although the combination therapy was generally well tolerated, it was associated with a significantly higher incidence of severe hypertension and diarrhea compared to both PARPi monotherapy and standard chemotherapy.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

Publications related to the thesis:

Baradács I, Teutsch B, Váradi A, Bilá A, Vincze Á, Hegyi P, Fazekas T, Komoróczy B, Nyirády P, Ács N, Bánhidy F, Lintner B. PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. J Ovarian Res. 2024 Feb 26;17(1):53. doi: 10.1186/s13048-024-01362-y. PMID: 38409030; PMCID: PMC10895809.

Baradács I, Teutsch B, Vincze Á, Hegyi P, Szabó B, Nyirády P, Ács N, Melczer Z, Bánhidy F, Lintner B. Efficacy and Safety of Combination Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2025 Mar 6;14(5):1776. doi: 10.3390/jcm14051776. PMID: 40095926; PMCID: PMC11901299.